

**Remarks:**

In the Office Action mailed on December 16, 2008, the Examiner rejected claims 1-6.

**In the Specification**

Applicant has submitted a substitute Specification to more clearly describe the invention. The changes made merely clarify that which may readily be discerned from the specification and drawings as originally filed. Accordingly, no new matter has been added.

**Status of the Claims**

Claims 1-6 were rejected in the Office Action. Claims XX are amended herein. Claims 1-6 are now pending in the application.

**The Claims**

**35 USC 103**

Claims 1-6 were rejected under 35 U.S.C. 103(a) as unpatentable over Fuji (XP-002198180, hereinafter "Fuji").

The Examiner argues that Fuji discloses a column for flash chromatography comprising granular and porous silica gel having 42  $\mu\text{m}$  granules with a pore size of 6nm. (Office Action page 2 Paragraph 2). The Examiner admits that Fuji does not disclose the 42  $\mu\text{m}$  granules being spherical or semi-spherical silica gel. (Office Action page 3 Paragraph 6). However, the Examiner then argues that the granular silica gel of Fuji would appear to be spherical since silica gel utilized in flash chromatography is generally spherical to allow for ease of packing. (Office Action, Page 4). It is noted by the Examiner that Applicant's Specification discloses spherical and semi-spherical porous silica gel comprised of

“granules” which would presumably be spherical or semi-spherical. The Examiner concludes that the silica gel granules of Fuji would be considered spherical no less than the silica of the Applicant’s disclosure (Office Action page 3, Paragraph 7).

Applicant respectfully disagrees. First, Applicant has amended the specification to more accurately reflect the original PCT application in terms of translating from the French. In the original, granule size was referred to as “granulometrie” which, unfortunately, was translated into “granules.” It appears that this mistranslation caused the Examiner to infer that Applicant implied that *spheres* and *granules* are the same. However, Applicant merely intended to indicate the relevant size by stating, e.g., “spherical and porous silica gel having granules of 25-40 $\mu$ .” After amendment, this and other similar uses have been amended to “spherical and porous silica gel having granulometry of 25-40 $\mu$ .” Thus, implying nothing other than that a particular granulometry is indicative of size and not shape.

Furthermore, the Examiner’s statement that “the granular silica gel of Fuji would appear to be spherical since silica gel utilized in flash chromatography is generally spherical to allow for ease of packing is inconsistent with the usage of the terms *granular* and *spherical* both in Fuji and in the related art. Applicant asserts that the *granular* silica gel of Fuji is not spherical but is that of an *irregular* shape. Page 2 of Fuji displays a table that compares the FL60D to the BW-300. The columns are specifically labeled as “Spherical” for the FL60D and “Granular” for the BW-300. (Fuji page 2 above the Loading amount and performance section). Fuji further mentions that the BW-300 is *normal* silica gel (Fuji, page 1 Separation of standard samples first sentence). In the field of flash chromatography, normal silica gel means silica gel of an irregular shape, which was commonly used for flash chromatography at the date of Fuji. The fact that the term “granular” is used by Fuji as a synonym of

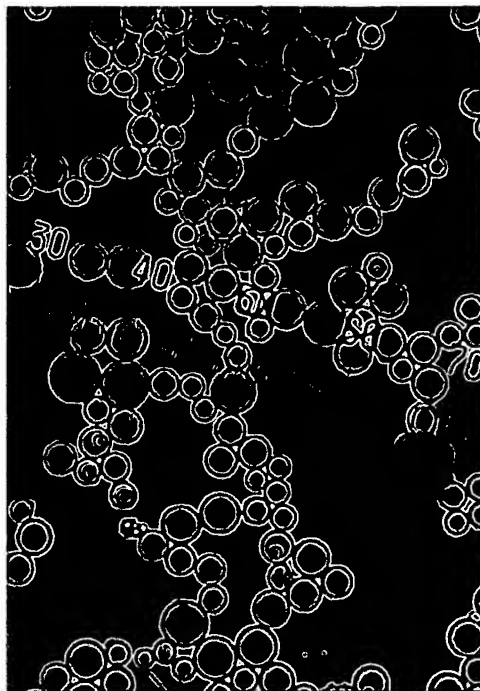
“irregular” can be deduced from the following statement in Fuji: “Since FL60D will be packed more homogeneously than granular silica gel, the column will exhibit higher performance and better reproducibility” (Fuji, page 2 Medium pressure chromatography, second sentence). The fact that granular silica gel is packed less homogeneously than spherical silica gel, directly and unambiguously implies that granular silica gel is of irregular shape. Conversely, since Fuji uses both the terms granular and spherical and appears to distinguish materials as being one or the other, it can only be inferred that when Fuji says *granular* that cannot mean *spherical* or vice versa. Thus, the Examiner’s statement that the “granular silica gel of Fuji would appear to be spherical” cannot be correct.

As further proof that the terms granular and irregular are synonyms in the general field of chromatography, consider the following.

In a web page related to the 2007 AAPS Annual Meeting and Exposition 11/10/2007-11/15/2007, located at <http://abstracts.aapspharmaceutica.com/expoaaps07/ec/forms/attendee/index.aspx?content=vbooth&id=1228> , in the section “Product Showcase”, subsection “Fuji Silysia Chemical’s Chromatorex Silica Gel” (Figure 1 Below), it is noted that “FSC offers irregular silica grades (Granular Silica-GS) ...” This clearly establishes that Fuji uses the terms “granular” and “irregular” as synonyms.

**Fuji Silysia Chemical's Chromatorex Silica Gel**

*The Premium Choice for Liquid Chromatography Silica Gel*



With 10 tons/day, Fuji Silysia is the world largest LC-producer, meeting the need at any scale, with consistent and reproducible quality, due to the highly pure sand used to produce the silica. FSC offers irregular silica grades (Granular Silica - GS), larger particle spherical silica grades (Micro-Bead - MB), and HPLC silica grades (Super Micro-Bead - SMB). FSC also offers DMPAM chiral, C4, C8, C18, CN, NH2, DIOL, and Phenyl bonded phases.

Product Brochure

[www.fuji-](http://www.fuji-silysia.co.jp/english/product/chromatography_silica/index.html)

[silysia.co.jp/english/product/chromatography\\_silica/index.html](http://silysia.co.jp/english/product/chromatography_silica/index.html)

Figure 1

United States Patent application number 11/772,799 (published under US 2008/0067343) states: "A silica gel which is most commonly employed as a chromatography support is a porous silica gel having a large number of pores on its surface. The particle may be in spherical shape or maybe granular (irregular shape)" (Paragraph 0030, first and second sentences). The 11/772,799 application further states that "[t]he shape and the uniformity of the particle ...such as spherical, rod-like granular form and the like, preferably a granular form (irregular shape) more preferably a granular silica gel modified with a quaternary ammonium group" (Paragraph 0032, second sentence).

United States patent no. 6,746,608 has a similar usage of the terms *irregular* and *granular*, namely: "Sphericity of the particles, rather than irregular, granular shapes, is advantageous (...)" (column 6, lines 9-10). It

should be noted that the '608 patent relates to high productivity liquid chromatography that requires mechanically strong support materials in order to withstand operation at high rates of flow under high pressures (column 1, lines 16-20). This type of chromatography is very different from flash chromatography, which uses weak support materials in the form of glass or plastic columns.

In conclusion, there is only one correct interpretation of the term *granular* (silica gel) in Fuji, namely that *granular* means *irregular* (silica gel), and, conversely, certainly not spherical or semi-spherical, which is the opposite of *granular*.

The issue then becomes whether a person of ordinary skill in the art would be motivated to modify the spherical silica gel of size 60  $\mu\text{m}$  (FL60D) to be of smaller size or modify the granular (irregular) silica gel of size 42  $\mu\text{m}$  (BW-300) to a spherical shape. Applicant has previously demonstrated, and the Examiner has acknowledged Applicant's evidence, that such would not be the case.

Applicant has previously demonstrated in the response dated December 10, 2008, that the invention claimed in the present application is non-obvious. Evidence was provided of a long-felt need and of unexpected results.

As discussed by Mr. Aznar in his declaration, there is a continuing desire in the art of flash chromatography to improve the resolution of the separation of materials found in a given sample as indicated by a theoretical plate number. This continuing desire to improve resolution of flash chromatography systems constitutes a long-felt need.

As set forth by Mr. Aznar, an unexpected result of the claimed invention, which involves using spherical or semi-spherical and porous silica gel having a granulometry between 3 and 45  $\mu\text{m}$ , is as follows. A remarkably higher resolution of the separation is achieved, while the back

pressure is sufficiently low to allow for the use of glass and plastic columns.

As further discussed in the Declaration of Mr. Aznar, an experiment was performed using equipment as used in Fuji but with spherical silica gel of relatively low granulometry and pores as claimed in the present application. These experiments reveal significant improvement over the results in Fuji. As mentioned hereinbefore there is a desire to improve the resolution of separation achieved by flash chromatography systems. Given this and the highly successful experimental results obtained by using spherical silica gel of relatively low granulometry as claimed in the present application, it follows that had the spherical silica gel of relatively low granulometry been obvious, a person of ordinary skill in the art would have already applied such silica gel and reported similarly good results.

However, adopting the relatively low granulometry for spherical silica gel is counter-intuitive to a person of ordinary skill in the art of flash chromatography. The rule is that a lower granulometry entails a higher back pressure, whereas the back pressure should be relatively low in the field of flash chromatography, in order to prevent columns, which are typically of glass or plastic, from breaking. A person of ordinary skill in the art would therefore not be motivated use spherical silica gel of relatively low granulometry.

However, Applicant found that spherical or semi-spherical silica gel having a granulometry comprised between 3 and 45  $\mu\text{m}$  provides unexpected results, namely a remarkably higher resolution of the separation, while the back pressure is sufficiently low to allow for the use of glass and plastic columns.

While arguably Fuji in different embodiments (FL60D and BW-300) discloses the size and shape claimed in Claims 1 and 2, that disclosure is not indicative of obviousness. While Fuji discloses spherical silica gel of larger granule size than that claimed (FL60D) and non-spherical

(irregular) silica gel of a size within the claimed size interval (BW-300), Fuji does not disclose a spherical silica gel with a granule size within the claimed size interval. One reference disclosing in different embodiments all elements of a claim does not lower the standard for obviousness. *Boston Scientific v. Cordis*, 2008-1073, slip op. at 17, Fed. Cir. January 15, 2009 ("Wolff teaches all of the limitations of claim 8, and the record did not contain substantial evidence for the jury to conclude otherwise. The only qualification to this statement of fact is that all of the limitations are found in two separate embodiments pictured side by side in the patent, not in one embodiment. However, '[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.' KSR, 127 S. Ct. at 1740.") As Applicant has demonstrated, a person of ordinary skill would not implement the claimed combination because the result is contrary to the predicted result of doing so.

Applying the factors set out in *Graham v. John Deere*<sup>1</sup> (cited with approval in KSR) one must conclude that based on the differences between the claimed invention and the content of the prior art, the level of ordinary skill in the art, and the provided secondary considerations of long felt need, and unexpected results, Applicants claimed invention is not obvious over Fuji.

Thus, for the reasons given above, Applicants respectfully request withdrawal of the rejection of Claims 1 through 6 and their early allowance.

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<sup>1</sup> *Graham v. John Deere Co. of Kansas City*, 383 U. S. 1, 17-18, set t an objective analysis for applying §103: "[T]he scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

The application is now deemed to be in condition for allowance and notice to that effect is solicited.

### CONCLUSION

It is submitted that all of the claims now in the application are allowable. Applicants respectfully request consideration of the application and claims and its early allowance. If the Examiner believes that the prosecution of the application would be facilitated by a telephonic interview, Applicants invite the Examiner to contact the undersigned at the number given below.

Applicants respectfully request that a timely Notice of Allowance be issued in this application.

Respectfully submitted,

Date: February 27, 2009

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